REMARKS

A detailed listing of all claims that are under examination in the application is presented above, with an appropriate defined status identifier. No amendments have been made to the claims with the current Reply. The listing of the claims provided above is solely for the convenience of the Examiner.

Claims 16-18, 20-25, and 27-30 are pending in the application, with claim 16 being the independent claim. Claims 1-15, 19, and 26 were cancelled by previous amendment without prejudice to or disclaimer of the subject matter therein.

Applicants respectfully request reconsideration of the present application in view of the reasons that follow.

I. The Double Patenting Rejection

The Examiner provisionally rejects claims 16-18 and 20-30 on the ground of nonstatutory obviousness-type double patenting as allegedly being unpatentable over claims 7, 19, 20, 23, and 27 of co-pending Application No. 10/498,215. (Office Action, at page 3, lines 1-3.)

Applicants note that claim 26 was cancelled by the Amendment and Reply Under 37 C.F.R. § 1.114 filed by Applicants on October 31, 2007.

With respect to claims 16-18, 20-25 and 27-30, Applicants respectfully request that the Examiner hold in abeyance the provisional obviousness-type double patenting rejection over claims 7, 19, 20, 23, and 27 of co-pending U.S. Appl. No. 10/498,215, which has not yet been examined on the merits. When a provisional obviousness-type double patenting rejection is the only rejection remaining, the Examiner should withdraw the rejection and allow the application to issue as a patent. *See* Manual of Patent Examining Procedure (MPEP), Eighth Ed., § 804, p. 800-17 (August 2007).

II. The Rejection of the Claims Under 35 U.S.C. § 103

The Examiner rejects claims 16-18 and 20-30 under 35 U.S.C. § 103(a) as allegedly being unpatentable over Okada *et al.*, U.S. Pat. No. 6,113,943 ("Okada") in view of Hutchinson, U.S. Pat. No. 5,889,110 ("Hutchinson"). Applicants respectfully traverse this rejection.

Specifically, the Examiner states that "[b]ased upon the beneficial overall teachings provided by Okada with respect to Hutchinson, Hutchinson discloses similar formulations can be manufactured using . . . either leuprorelin or buserelin and continuous release over a relatively long period of time of up to 6 months." (Office Action, at page 4, line 21, to page 5, line 2.) The Examiner further states that "Okada discloses the dose of the sustained release preparation per administration for one month in terms of a physiologically active range . . . ." (Office Action, at page 5, lines 2-4.) The Examiner concludes that "it is apparent that one of ordinary skill in the art would have had a reasonable expectation of success in producing the claimed invention" and, therefore, "the invention as a whole was *prima facie* obvious to one of ordinary skill in the art at the time the invention was made, as evidenced by the references, especially in the absence of evidence to the contrary." (Office Action, at page 5, lines 5-9.)

As discussed in Applicants' Amendment and Reply Under 37 C.F.R. § 1.114, filed on October 31, 2007, the present invention as claimed is directed to a sustained release preparation comprising a combination of first microcapsules which gradually release a GnRH agonist or a salt thereof for 5 months or longer, and second microcapsules which gradually release a GnRH agonist or a salt thereof for shorter than 5 months. As shown in the examples of the present application, the sustained-release preparations of the invention provide an improved blood concentration pattern for the released GnRH agonist because they release an increased amount of the agonist at an early stage of administration (e.g., at about one week) while exhibiting stable sustained-release over a long term. See Experimental Examples 1-3, at pages 83-85 of the specification as filed.

In particular, independent claim 16, the claim having the broadest scope, recites that the GnRH agonist is released *"so that blood concentration of the GnRH agonist within one*

week after administration is about 2 ng/mL or higher." All remaining pending claims in the application depend from claim 16 and thus incorporate this element.

As discussed in the Applicants' previous responses, in neither Okada nor Hutchinson is there a showing of a blood concentration pattern of the active agent after administration of one of the disclosed sustained release preparations.

Okada fails to teach specific blood concentration patterns produced by the disclosed sustained release preparations. See, for example, Experimental Example 4 (Okada, at column 25), which merely discloses the amount of drug (leuprorelin acetate) that remains subcutaneously after administration of a sustained-release preparation of the invention. There is no disclosure of the resulting blood concentration of the drug released from the preparation.

Hutchinson fails to cure the deficiencies of Okada. Hutchinson merely discloses a releasing "term" based on a pharmacological effect and also fails to disclose a blood concentration pattern or even a release pattern (see, e.g., Hutchinson, in Examples 16-20, at columns 37-41). Although each of these examples in Hutchinson concerns blood concentrations, neither contains meaningful data from which to form a prediction, regardless of whether or not Okada teaches blood concentrations.

Thus, because neither Okada nor Hutchinson disclose blood concentration patterns of the active agent after administration of the sustained-release preparations, it would be difficult to design a sustained-release preparation exhibiting the specific blood concentration pattern recited in the present claims. Applicants submit that, even if Okada and Hutchinson were combined, there would have been no reason for one of skill in the art to combine two kinds of preparations to arrive at the sustained-release preparation as presently claimed that exhibits the recited improvement in the blood concentration pattern of a GnRH agonist (*i.e.*, a sustained-release preparation that releases a GnRH agonist such that the blood concentration of the GnRH agonist within one week after administration is about 2 ng/mL or higher). Thus, Applicants submit that, at the time of the invention, the claimed sustained release preparations would not have been obvious in light of Okada and Hutchinson.

In addition, Applicants wish to point out to the Examiner the difficulties in designing sustained-release preparations. For example, designing a 6 month sustained-release preparation is quite different from designing a 1 month sustained-release preparation. That is, for a 1 month sustained-release preparation, the rate of drug release is about 3.3% per day (*i.e.*, 100% ÷30 days = about 3.3%), while, for a 6 month sustained-release preparation, the rate of drug release is about 0.5% per day (*i.e.*, 100% ÷ 182 days = about 0.5%). As the desired length of a sustained-release period becomes longer, the daily rate of drug release must be controlled within a narrower range, which becomes increasingly difficult.

In the present invention, Applicants have overcome this difficulty by combining microcapsules which release the active components for a short term and microcapsules which release the active components for a long term. Although it is known that, even if sustained-release preparations disclosed in the prior art references are combined, a daily drug-release rate cannot be controlled within the desired narrow range to maintain a blood concentration of the active component at a certain level, Applicants have managed to provide sustained-release preparations in which the daily drug-release rate can be controlled within a narrower range by using the specific combination of microcapsules according to the present invention.

Applicants submit that the rejection of claims 16-18 and 20-30 under 35 U.S.C. § 103(a) has been overcome and respectfully request that the Examiner withdraw the rejection.

CONCLUSION

Applicants believe that the present application is now in condition for allowance. Favorable reconsideration of the application as amended is respectfully requested.

The Examiner is invited to contact the undersigned by telephone if it is felt that a telephone interview would advance the prosecution of the present application.

The Commissioner is hereby authorized to charge any additional fees which may be required regarding this application under 37 C.F.R. §§ 1.16-1.17, or credit any overpayment, to Deposit Account No. 19-0741. Should no proper payment be enclosed herewith, as by a

check or credit card payment form being in the wrong amount, unsigned, post-dated, otherwise improper or informal or even entirely missing, the Commissioner is authorized to charge the unpaid amount to Deposit Account No. 19-0741. If any extensions of time are needed for timely acceptance of papers submitted herewith, Applicants hereby petition for such extension under 37 C.F.R. §1.136 and authorizes payment of any such extensions fees to Deposit Account No. 19-0741.

Respectfully submitted,

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